"UNDERSTAND THE SCIENCE ON ASBESTOS"
OUTLINE
October 5, 1999

Objective: Share understanding of science regarding asbestos: Know, Known, Unknown

1. Background

   - Experience
   - Properties, Production & Use[1]

2. Causation Analysis[2] [3]

   - Strength of association*
   - Consistency*
   - Specificity*
   - Temporal relationship*
   - Dose-response relationship*
   - Biological plausibility*
   - Animal studies
   - QSAR
   - Confounders
   - Coherence*

3. Effects[4]

   - *Asbestosis*
   - *Bronchogenic carcinoma*[5]
   - *Malignant mesothelioma*
   - Cancer - other[6] [7]

4. Discussion & Conclusions

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[1] *Documentation of TLVs and BEIs*, American Conference of Governmental Industrial Hygienists, Cincinnati OH (1999)
[2] Hill, A.B., *The Environment and Disease: Association or Causation?* Proceedings of the Royal Society of Medicine, Section of Occupational Medicine 295 (1965)
[3] Office of Research and Development, EPA, Working Paper for Considering Draft Revisions to the U.S. EPA Guidelines for Cancer Risk. EPA/600/AP-92/003 (1992)
[4] Robbins, S.T. & R.S. Cotran, PATHOLOGIC BASIS OF DISEASE. Philadelphia: W.B. Saunders Co. (1999)
[5] http:ntp-server.niehs.nih.gov/htdocs/8_RoC/KC/Asbestos.html
[6] Schottenfield, D. & J.F. Fraumeni, CANCER EPIDEMIOLOGY AND PREVENTION, New York: Oxford University Press (1996)
[7] Lee, P.N., *A review of evidence on the joint relationship of asbestos exposure and smoking to risk of lung cancer.* P.N. Lee Statistics and Computing LTD, Surrey UK (1999)

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SOME IMPORTANT QUESTIONS

ASBESTOS

- What is asbestos? What does is look like (macro/micro)? What are physical/chemical characteristics? Use?
- What are fiber compositions and dimensions of biological significance?
- What are the primary routes of exposure and outcomes?
- Are there dose-response, time frequency/duration, and reversible relationships?
- Is one disease state a precursor to other states?
- Do you need asbestosis as a precursor to lung cancer? (Oska – Progression of Asbestosis Predicts Lung Cancer, Hughes/Weill)
- Is there a higher incidence of lung cancer in people with asbestosis?
- How are fiber eliminated? How do they get into pleura? Are they inside the tumors?
- What are the etiologies with each disease?
- Are disease dose/time dependent? Reversible? Slope factors?
- Are disease states cell specific or dependent on other factors?
- Is Disease State dependent on fiber type, dimension, and composition?
- Are animal and human data consistent?
- Do other substances have similar etiologies?
- What is/are the basis of regulatory/occupational standards? ACGIH/MAK (British Occupational
- Is asbestos genotoxic *invitro*?

ASBESTOS & SMOKING

- Define interaction: (Rothman, Steenland, Berenbaum)
- If conclusions of interaction between asbestos & smoking lung cancer are model dependent, which model should be chosen?
- Why do epidemiologists use a multiplicative model and public health authorities use an additive model?
- Which model does asbestos and smoking "best fit?"
- Is it possible to attribute risk between cancer associated with smoking vs. asbestos exposure?
- Do lung fiber loads differ between non-smoking and smoking asbestos exposed individuals?
- What is the significance of lung clearance between non-smoking and smoking asbestos exposed individuals?
- Is there a difference in cell type between lung cancers strictly associated with smoking vs. asbestos exposures?
- Is there a mechanism of interaction between smoking and asbestos exposures? How is this mediated? (Kamp/BT Mossman/Miller in U.K.)
- Is it possible to attribute risk of one exposure (asbestos) from another exposure (smoking)?

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ASBESTOS REVIEW

"Asbestos is a tremendous health hazard"[8]. Asbestos has been identified as a complete carcinogen in variety of studies with sufficient evidence as a human and animal carcinogen[9]. Commercial use of asbestos in the U.S. rose from 120,000 tons in 1930 to 857,000 tons in 1973. In the U.S. alone about 500 factories employed 31,000 workers to manufacture 3000 different articles of asbestos. An additional 5 million workers in the construction industry have had greater than two asbestos fibers/cc exposures in the workplace. Mineral fibers represent the greatest cause – after cigarette smoke – of respiratory cancer due to air pollutants.

Past asbestos exposure may currently account for 2000 mesothelioma deaths per year and 4000 to 6000 lung cancer deaths per year. All major commercial types of asbestos (crocidolite, amosite, and chryotile) can cause each of the major asbestos-related respiratory diseases. Lung cancers in asbestos-exposed individuals probably do not have different distribution of histological types from that of non-asbestos-related lung cancers. Although earlier studies showed prevalence for lower lobe (adenocarcinoma) involvement with severe fibrosis and twice the rate as those found in smokers. Smoker without asbestos exposures were twice as often to have tumors associated with the uppers lobes of the lungs in comparison with asbestos exposed workers. Nonoccupational exposures are likely to be associated with malignant disease outcomes qualitatively similar to those associated with occupational exposures.[10] Asbestosis patients with radiographic progression of small opacity profusion over a few years are at a higher risk of lung cancer than those with a less aggressive course of the disease.[11]

Occupational exposures to asbestos, cotton dust, coal dust and flour dust have long been implicated in the etiology of lung disease. In addition to these four natural substances, various man-made mineral fibers have been investigated as causes of lung disease, including fiberglass, ceramic "whiskers" and other glass filaments.
Asbestos (from the Greek, "inextinguishable" or "indestructible") is a commercial term for not one, but six, naturally occurring minerals:

- Chrysotile
- Amosite (grunerite asbestos)
- Crocidolite (riebeckite asbestos)
- Anthophyllite asbestos
- Tremolite asbestos
- Actinolite asbestos

It may be important to note here that not all of these have been equally implicated in the induction of lung disease. Crocidolite and amosite are reported to be more potent initiators of mesotheliomas, for example.

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[8] Greenberg, SD, Cytopathology and Asbestos-Associated Disease. Pp. 223 (1992)
[9] NTP 8th ROC, http://ntp-server.niehs.nih.gov/htdocs/8_RoC/KC/Asbestos.html
[10] Omenn, GS, J. Merchant, E. Boatman, JM Dement, M. Kuschner, W. Nicholson, J. Peto, and L. Rosenstock. Contribution of Environmental Fibers to Respiratory Cancer. Env. Health Perspectives 70: pp. 51-56 (1986)
[11] Oksa, P., M. Klockers, A. Karjalainen, MS Huuskonen, K. Vattulainen, E. Pukkala, and H. Nordman. Progression of Asbestosis Predicts-Lung Cancer. Chest 113:6 pp. 1517-1521 (1998)

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Three distinct disease states have been associated with asbestos:

- **Asbestosis** – a disease of the lungs characterized by the presence of scar tissue (i.e., fibrosis) resulting specifically from the inhalation of asbestos fibers.
- **Bronchial carcinoma** – lung cancer
- **Mesothelioma** – a rare form of malignancy arising from the mesothelium, which is the epithelial tissue enveloping the lungs and lining the thoracic cavity and the abdominal cavity.[1]

There is disagreement among experts regarding the pathogenesis of each of these disease states. One factor contributing to the confusion about specific etiology is that asbestos related lung disease could appear after a latency of 10 to 40 years from first exposure.[2]

The size of the fiber is also a factor. According to most general reviews on the subject, long, thin fibers (a length of more than 5μm, a diameter of less than 3 μm) are more harmful than shorter fibers. Fibers with maximum carcinogenic potential are longer than 8μm and less than 1.5μm in diameter.[3] There have been recent discussions on the importance of fiber dimension to disease pathogenesis, e.g.,

"Exposure assessment for airborne man-made mineral fibres: the role of fibre dimensions," by F. S. Rosenthal, Annals of Occupational Hygiene, 37(4): 395-417, August 1993.

> Environmental exposures to man-made mineral fibres (MMMF) typically contain fibres which are polydisperse with respect to fibre dimensions. Fibre dimensions may influence their biological action through effects on: the efficiency of transport to target tissues; the residence time in target tissues; and the biological activity vs. fibre dimensions should be accounted for when assessing exposure for epidemiological studies of the risk of cancer in subjects exposed to MMMF. In order to provide insight into the influence of fibre dimensions on the potential carcinogenicity of MMMF, this paper reviews literature concerning the sites of lung tumours, regional fibre deposition, biological effects of fibres in in vivo and in vitro systems, dissolution rates of fibres and rates of physiological clearance of inhaled particles. **Tumorigenicity of fibres in contact with target tissue appears to be primarily a function of fibre length, whereas both fibre diameter and fibre length may affect the penetration of fibres through the respiratory tract as well as their residence time in target tissues.**[4] A methodology is presented to use this information to compute estimates of biologically effective exposure from the joint distribution of fibre lengths and diameters found in an environmental exposure.

[1] Encyclopedia of Human Biology, V.1, "Asbestos," by Jacques Dunnigan, p. 417-425, New York, Academic, 1991.
[2] "Clinical controversies in asbestos-induced lung diseases." By Hyers-TM; Ohar-JM; Crim-C in *Seminars in Diagnostic Pathology*; 9(2): 97-101, May 1992.
[4] Emphasis mine.

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Whether fibrosis is a prerequisite for carcinogenicity is also an open issue. The presence of asbestos bodies in the lung indicates exposure to asbestos. These bodies were first described in the early 1900's, and they can be present in the lungs of workers who do not have asbestosis. The bodies are formed when the inhaled fiber becomes covered with a layer of iron-protein-mucopolysaccharide material. A number of different types of fibrous dust (fibrous aluminum silicate, silicon carbide whiskers, cosmetic talc, and fibrous glass) can also form these "bodies." The term "ferruginous body" is used when the fiber forming the core is unknown. Some examples of other fibers, which cause these formations in the lung, are:[5]

- **sheet silicates** (talc, mica, or kaolinite) found in the lungs of roofer, rubber factory workers, shipyard welders
- **carbon fibers** (from coal) found in the lungs of coal miners and in at least one instance in the lungs of a person exposed to wood stove dust
- **metal oxides** (titanium, iron, aluminum, chromium) found in the lungs of shipyard welders, iron reclamation facility workers, metal polishers
- **man-made mineral fibers** (fibrous glass)
- **diatomaceous earth**
- **zeolites** (naturally occurring hydrated aluminum silicates)
- **Silicon carbide whiskers**

A report of the WHO working group entitled "Asbestos and other natural mineral fibres"[6] notes some specific mineral fibers with this comment:

> Few data are available concerning the pathogenicity of the other natural mineral fibres. Fibrosis in rats has been observed following inhalation of **attapulgite** and **seplolite**; a remarkably high incidence of mesotheliomas occurred in rats following inhalation of **erionite**. Long-fibred **attapulgite** induced mesotheliomas following intrapleural and intraperitoneal administration. **Wollastonite** also induced mesothelioma after intrapleural administration. **Erionite** induced extremely high incidences of mesotheliomas following inhalation exposure and intrapleural and intraperitoneal administration.

It may be important to note here that individuals can have asbestos bodies present in the lungs and be asymptomatic, i.e., have no symptoms of disease. In their review of asbestosis Roggli and Pratt note that the "mechanisms by which asbestos produces tissue injury are incompletely understood."[7] There is a substantial body of recent work discussing the pathogenesis of lung disease induced by asbestos. There are at least two mechanisms proposed for the causative path of fibrosis:

> One.... Those toxic oxygen radicals generated on fiber surfaces and/or intracellularly are the central mediators of disease. The second hypothesis is not mutually exclusive of the first, but, in my opinion, may be integral to it, i.e., the cellular injury induced by oxygen radicals stimulates the elaboration of multiple

[5] Described in detail in "Asbestos bodies and nonasbestos ferruginous bodies," by Vivtor L. Roggli, Chapter 3: Pathology of Asbestos-Associated Diseases by Roggli, et al., Little, Brown, 1992.
[6] "Asbestos and other natural mineral fibres," WHO-working-group, Environmental health criteria; 53, 194 p. 1986.

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> varieties of growth factors and cytokines that mediate the pathogenesis of asbestosis. There is increasing evidence that molecules such as platelet-derived growth factor and transforming growth factor beta, both synthesized and secreted by activated lung macrophages, are responsible, respectively, for the increased interstitial cell populations and extracellular matrix proteins that are the hallmarks of asbestos-induced fibrosis. The challenge today is to establish which combinations of the many factors released actually are playing a role in disease pathogenesis.[8]

The mechanisms for development of carcinomas are also still under discussion, e.g.,

> Asbestos fibers may exert their carcinogenic effects on mesothelial cells and bronchial epithelial cells by direct and indirect mechanisms. Direct effects can occur following the physical interaction of fibers with target cells or by the generation of free radicals from the fiber surface; indirect effects, following the interaction of fibers with inflammatory cells can result in the production of cellular mediators such as cytokines and various reactive oxygen species. As a result, target cells may be induced to proliferate and/or sustain genetic alterations, which lead to tumor development.[9]

It should also be noted that the presence of asbestos fibers in the urban environment is ubiquitous. Environmental exposure in air and water is usually to fibers shorter than the lengths implicated in disease states. The concentration of asbestos fibers in the urban atmosphere is in the range of 10-100ng/m3.[10] The fibers also occur in drinking water in the range of 200,000 to 2,000,000 fibers per liter.

Lung cancer: Asbestos & Smoking: Lung cancer risk is increased and decreased in association with various activities, exposures and social-economic status. Lung cancer risk is commonly determined in epidemiology by using statistical methods that multiply the entire associated risk factors together (multiplicative model). This model tests the hypothesis that there is no "interaction" between the various exposures, that each risk factor is independent and that each factor is not modified by the other.

> *Epidemiology studies have shown that asbestos and smoking can independently increase the risk of lung cancer. Depending on the nature and extent of the asbestos exposure, asbestos exposure increases lung cancer risk an overall 2 to 5-fold. Asbestos exposure increases lung cancer risk similarly in nonsmokers or smokers. Depending on the nature and extent of smoking, smoking increases lung cancer risk an overall 1 to 10-fold. Smoking increases lung cancer risk similarly in non-asbestos or asbestos exposed workers. Thus, asbestos exposure increases lung cancer risk an overall 2 to 5-fold regardless of smoking; and, smoking increases lung cancer risk an overall 1 to 10-fold regardless of the asbestos exposure.*

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[8] "Asbestos-induced lung disease," by A.R. Brody, Environmental Health Perspectives, 100:21-30, April, 1993.
[9] "Possible cellular and molecular mechanisms for asbestos carcinogenicity," by C. Walker, J. Everitt and J.C. Barrett, American Journal of Industrial Medicine, 21(2): 253-73, 1992.
[10] Ullmann's Encyclopedia of Industrial Chemistry, 5th ed., V.A3, "Asbestos," by Seymour S. Chissick, pp. 151-167.

Source: https://www.industrydocuments.ucsf.edu/docs/mqcl0001